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Chemistry Letters

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Advance Publication on the web March 2, 2018

doi:10.1246/cl.180123

Copper- and Borinic Acid-Catalyzed Propargylic Etherification of Propargylic Carbonates with Benzyl Alcohols

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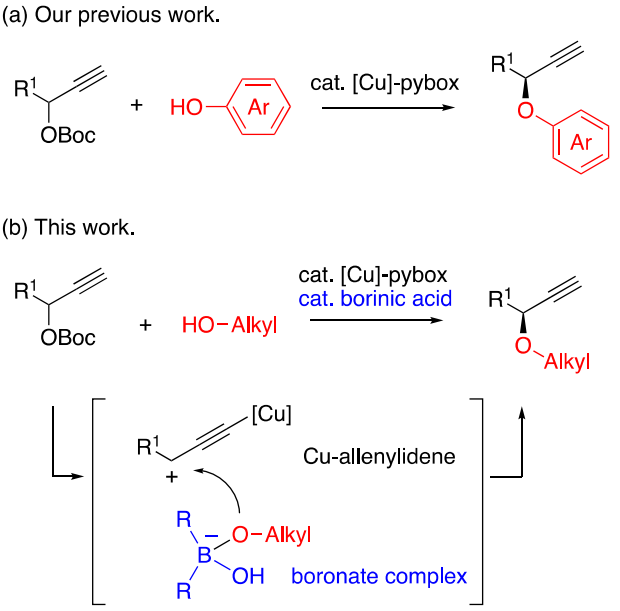
Propargylic substitution reactions have offered useful synthetic methods because further transformations based on the alkyne moiety in the propargylic substituted products was readily achieved to construct more complex organic compounds. A large number of works have been devoted to enantioselective propargylic substitution reactions with a variety of nucleophiles. However, successful examples of the use of alcohols as nucleophiles have been quite limited until now. To achieve utilization of aliphatic alcohols, herein we report the use of combined catalysis of a copper-pybox complex and a borinic acid. In this catalytic system, aliphatic alcohols such as benzyl alcohol derivatives were successfully applied to afford the corresponding propargylic etherified products in good yields with high enantioselectivities.

Keywords: Propargylic etherification, Copper catalyst, Borinic acid

Enantioselective substitution reactions at carbon centers adjacent to an alkyne moiety, that is, propargylic substitution reactions have attracted outstanding interest in organic chemistry because of the high utility for subsequent transformations of the alkyne moiety.[1] In 2008, van Maarseveen and co-workers[2] and our group[3,4] independently reported copper-catalyzed enantioselective propargylic substitution reactions of propargylic alcohol derivatives. After these reports, the copper-catalyzed reaction systems have been extensively studied to allow the use of various nucleophiles for the last decade.[5,6]

Despite the eager studies by several groups, enantioselective propargylic substitution reactions with alcohols as nucleophiles have not been achieved until recently. Our group reported the first successful example of the enantioselective propargylic etherification with the use of copper-pybox system (Scheme 1a).[3d] However, the applicable alcohols were limited to phenol derivatives, otherwise an excess amount of simple alcohols (methanol and ethanol) as solvents is necessary to promote catalytic reactions.

To improve the utility of aliphatic alcohols, we focused on combination of copper and boron catalysts. Recently, boron compounds have been successfully employed to activate alcohols as nucleophiles by formation of boronate.[7] This activation mode was expected to be useful to promote the propargylic substitution reactions with aliphatic alcohols. Meanwhile, during our investigation of the present work, Niu and coworkers independently reported the copper- and borinic acid-catalyzed propargylic etherification reactions.[6] In this reaction system, however, available alcohols have been limited to diols and polyols, which may coordinate the boron center in a bidentate fashion. Complementary to our[3d] and Niu's[6] works, we have found the copper- and borinic acid-catalyzed reaction system is available toward the use of monodentate alcohols such as benzyl alcohols (Scheme 1b). Herein, we report preliminary results.

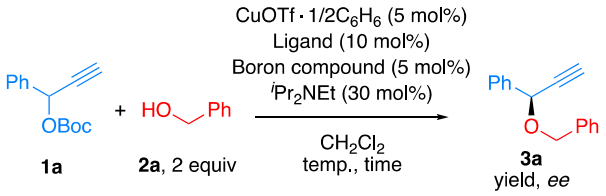


Scheme 1. Enantioselective propargylic etherification with aromatic and aliphatic alcohols.

The initial investigation on the reaction conditions was carried out with *tert*-butyl 1-phenyl-2-propyn-1-yl carbonate (**1a**) and benzyl alcohol (**2a**) as typical substrates (Table 1). At first, the reaction using the copper-pybox complex as a sole catalyst was tested under the conditions similar to our previous work (Table 1, Entry 1).[3d] In this case, no etherification product (**3a**) was observed. Next, we investigated the combination of the copper-pybox complex with a boron compound. The reaction of **1a** with **2a** was carried out in the presence of copper(I) trifluoromethanesulfonate benzene complex (5 mol% based on Cu atom), (*S*)-Ph-pybox ligand **L1** (10 mol%),[8] 3,5-bis(trifluoromethyl)phenylboronic acid (**B1**) (5 mol%), and Hünig's base (30 mol%) (Table 1, Entry 2). Fortunately, the desired propargylic ether **3a** was obtained in 68% yield with 89% ee (*R*). Encouraged by this result, we tested other boron compounds. Among the tested boron compounds: boronic acids (Table 1, Entries 3-5), bis(neopentyl glycolato)diboron (Table 1, Entry 6), dichlorophenylborane (Table 1, Entry 7), borinic acids (Table 1, Entries 8-10), and a fused triphenyl borane derivative (Table 1, Entry 11), some boronic and borinic acids were revealed to be

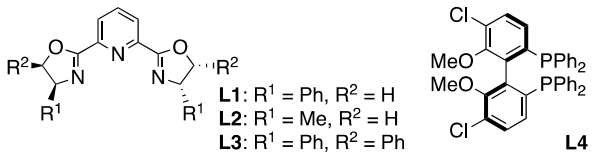
effective; the highest enantioselectivity was observed when using the dibenzo-1,4-oxaborine-derived borinic acid **B2** (Table 1, Entry 9). Then, we examined the choice of the pybox ligand. The use of (*S*)-Me-pybox ligand (**L2**) which was the optimized ligand in our previous work[3d] gave **3a** in good yield but with slightly lower enantioselectivity (Table 1, Entry 12). On the other hand, the diPh-pybox **L3** exhibited poor reactivity (Table 1, Entry 13). We also

Table 1. Reactions of *tert*-butyl 1-phenyl-2-propyn-1-yl carbonate (**1a**) with benzyl alcohol (**2a**).

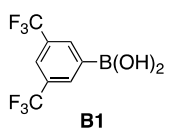


1a **3a** yield, *ee*

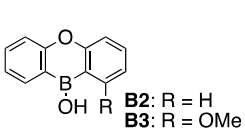
Entry	Ligand	Boron compound	Conditions	Yield (%)[b]	*Ee* (%)[c]
1	**L1**	-	rt, 24 h	0	-
2	**L1**	**B1**	rt, 4 h	68	89
3	**L1**	$PhB(OH)_2$	rt, 3 h	65	91
4	**L1**	$C_6F_5B(OH)_2$	rt, 24 h	0	-
5	**L1**	$CyB(OH)_2$	rt, 24 h	0	-
6	**L1**	$B_2(neo)_2$	rt, 24 h	0	-
7	**L1**	$PhBCl_2$	rt, 2 h	0	-
8	**L1**	Ph_2BOH	rt, 24 h	34	92
9	**L1**	**B2**	rt, 3 h	62	95
10	**L1**	**B3**	rt, 24 h	0	-
11	**L1**	**B4**	rt, 6 h	51	84
12	**L2**	**B2**	rt, 7 h	85	80
13	**L3**	**B2**	rt, 34 h	trace	-
14	**L4**	**B2**	rt, 4 h	0	-
15	**L1**	**B2**	–10 °C, 48 h	92	97



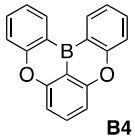
L4



B1



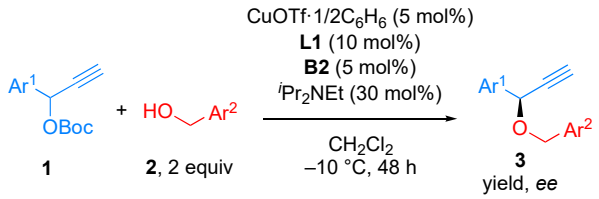
B2: R = H
B3: R = OMe



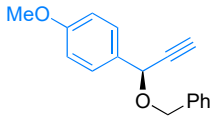
B4

[a] All reactions of **1a** (0.200 mmol) with **2a** (0.400 mmol) were carried out in the presence of $CuOTf{\cdot}1/2C_6H_6$ (0.010 mmol), a ligand (0.020 mmol), a boron compound (0.010 mmol), and $^iPr_2NEt$ (0.067 mmol) in CH_2Cl_2 (2.0 mL) at the indicated conditions. [b] Isolted yield. [c] Determined by chiral HPLC analysis.

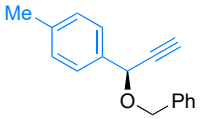
Table 2. Reactions of propargylic carbonates (**1**) with aliphatic alcohols (**2**).



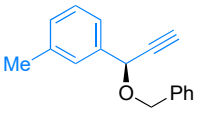
1 **2**, 2 equiv **3** yield, *ee*



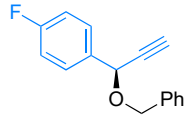
3b, 75% yield, 95%ee



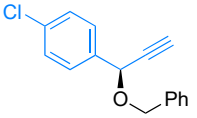
3c, 95% yield, 91%ee



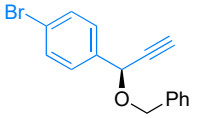
3d, 75% yield, 97%ee



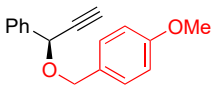
3e, 50% yield, 95%ee



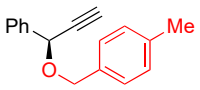
3f, 84% yield, 98%ee



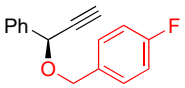
3g, 45% yield, 96%ee



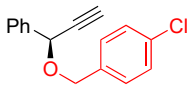
3h, 45% yield, 96%ee



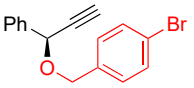
3i, 84% yield, 96%ee



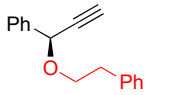
3j, 65% yield, 96%ee



3k, 74% yield, 96%ee



3l, 60% yield, 97%ee



3m, 67% yield, 74%ee

[a] All reactions of propargylic carbonate **1** (0.200 mmol) with aliphatic alcohol **2** (0.400 mmol) were carried out in the presence of $CuOTf{\cdot}1/2C_6H_6$ (0.010 mmol), **L1** (0.020 mmol), **B2** (0.010 mmol), and $^iPr_2NEt$ (0.067 mmol) in CH_2Cl_2 (2.0 mL) at –10 ºC for 48 h. [b] Isolted yield. [c] Determined by chiral HPLC analysis.

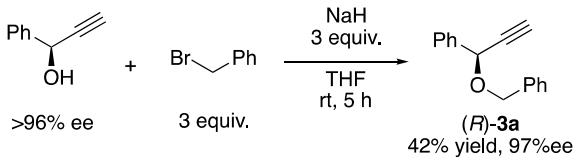
examined chiral diphosphine ligand **L4**, which effectively worked in propargylic amination,[3a,b] but no **3a** was observed (Table 1, Entry 14). Finally, lowering the reaction temperature to –10 ºC successfully produced **3a** in satisfactory yield with the highest enantioselectivity (92% yield, 97% ee) (Table 1, Entry 15).

With the optimized reaction conditions in hand, the reactions of various propargylic carbonates were examined (Table 2). Propargylic carbonates bearing electron donating

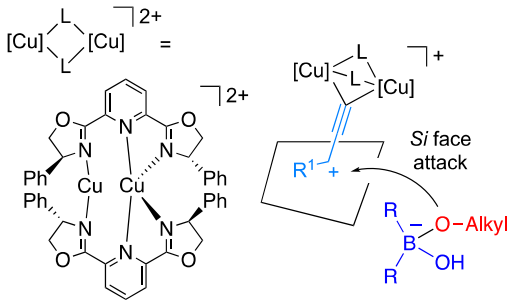
and withdrawing substituents at the *para*-position of the benzene ring in **1** were successfully transformed into the corresponding propargylic etherified products (**3b**, **3c**, and **3e-g**) in moderate to high yields with an excellent enantioselectivity. Introduction of a methyl group at the *meta*-position, which might change the steric environment around the chiral center, also produced the desired product (**3d**) with a similar enantioselectivity.

Next, the use of benzyl alcohol derivatives was investigated. Benzyl alcohol derivatives with methoxy, methyl, fluoro, chloro, and bromo substituents at the *para*-position of the benzene ring in **3** (**3h-l**) were available in this reaction system. An aliphatic alcohol with a longer alkyl chain, 2-phenylethanol, was transformed into **3m** in good yield but with a slightly lower enantioselectivity (74% ee).

The absolute stereoconfiguration of the propargylic etherification product **3a** was confirmed by comparison with the separately prepared (*R*)-**3a** from commercially available (*R*)-1-phenyl-2-propyn-1-ol. Treatment of the (*R*)-1-phenyl-2-propyn-1-ol with sodium hydride and benzyl bromide afforded (*R*)-**3a** without loss of the optical purity (Scheme 2). By comparison of the HPLC analyses, we confirmed the (*R*)-isomer of **3a** was the major product under the present copper-pybox- and borinic acid-catalysis.



Scheme 2. Preparation of propargylic ether **3a** with unambiguous stereoconfiguration.



Scheme 3. Plausible enantio-induction step.

The (*R*)-selective product formation by using (*S*)-pybox ligands as the chiral source is same to the previous propargylic etherification with aromatic alcohols and diols, indicating a similar transition state on the enantio-induction step to the previous work.[3d,3e] At present, we consider the present etherification proceeds via a similar pathway to our previous work, where nucleophilic attack of an alcohol toward a dimetallic copper-allenylidene complex derived from $[Cu_2(\mathbf{L1})_2][OTf]_2$,[9] which is generated in situ from $CuOTf{\cdot}1/2C_6H_6$ and 1 equiv of **L1**, from *Si* face of the allenylidene ligand is a key step,[3d] although the alcohol is presumably activated by forming boronate complex[10] in the present reaction system (Scheme 3). Similar pathways have been proposed by other research groups.[6]

In summary, we have developed a copper- and borinic acid-catalyzed reaction system that furnishes propargylic etherification products with aliphatic alcohols as nucleophiles in good yields with excellent enantioselectivities. We also revealed the monodentate alcohols were effectively activated by the borinic acid catalyst probably due to formation of the boronate complex in a similar manner to diols and polyols. We believe that the present findings may be further applicable in a variety of reaction systems.

Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

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